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THE PATHOLOGY OF LABIAL AND NASAL HERPES AND OF HERPES OF THE BODY OCCURRING IN ACUTE CROUPOUS PNEUMONIA, AND THEIR RELATION TO THE SO-CALLED HERPES ZOSTER.[1]

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OUR knowledge of herpes zoster was very much extended by the recent contribution of Head and Carpenter.[2] These authors showed, among other things: 1. That herpes zoster (in 18 cases, at least) is associated with destructive, and usually inflammatory, changes in the sensory ganglia (posterior root or Gasserian) corresponding to the nerve supply of the part affected with herpes. 2. That in recent cases (before the eleventh day) degenerative changes are not demonstrable in either the peripheral nerves, the posterior root fibres, or the central nervous system. 3. That in cases examined after the lapse of this period degenerative changes are present in these structures and apparently correspond to the affected areas in the ganglia. Their work was based upon the study of 21 cases in all stages of the eruption. They state that before their own work there were only two well-reported autopsies on cases of herpes ophthalmicus (Wys and Sattler) and five satisfactory reports on zoster of the trunk (Lesser, Chandelux and Dubler). Von Bärensprung's oft-quoted case is classified as unsatisfactory, because, though he noted the occurrence of hemorrhage into a ganglion, he failed to mention to which of the three ganglia removed he alluded.

While this valuable communication has placed our knowledge of herpes zoster on a substantial basis, it is clear that more light is needed upon the etiological factors concerned, as well as upon the identification and classification of the various types of herpes.

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[1] Read at the Seventeenth Annual Meeting of the Association of American Physicians, held in Washington, D. C., 1902.

[2] Brain, Autumn, 1900.

In order to clearly understand our present knowledge on the subject, the following summary of the main facts may be helpful. There are a number of clinical and apparently several anatomical types of herpes: herpes zoster involving the neck, trunk, and extremities (following the distribution of the spinal posterior root ganglia); herpes ophthalmicus (following the distribution of the first division of the fifth or trigeminal nerve, Gasserian ganglion); herpes facialis, herpes labialis et nasalis (probably following the distribution of the second and third divisions of the trigeminal nerve, but unsupported at this time by anatomical observations), and herpes genitalis (commonly believed to be due to local irritation and not known to be associated with any lesion of the nervous system).

The herpes facialis, labialis, nasalis, and genitalis are classed by Hartzell[1] as herpes simplex, in contradistinction to herpes zoster of the neck, trunk, extremities, and ophthalmic area (herpes zoster ophthalmicus). These latter forms of herpes have been shown to be identical in that they are associated with the same lesions of the nervous system (especially those of the sensory ganglion), and the changes in the skin are believed to be the same.

It seems further to have been conclusively demonstrated that the lesions of the skin are secondary to the primary changes in the corresponding sensory ganglia, which in turn may be brought about by a variety of causes. The cases, however, may be classified into the primary or spontaneous herpes zoster, in which the affection is apparently primary and not due to any evident preceding infection or injury, and the secondary form, in which there is more or less clear evidence that the disease occurs as the sequel or complication of some antecedent affection, as pneumonia, cerebro-spinal meningitis, etc., or to injury.

Our knowledge of the changes in the skin in the various clinical forms of herpes is far from satisfactory. Not until a sufficient number of careful observations upon the histological changes in all the stages of each variety of herpes is available will we be in a position to compare critically the processes, and, perhaps, distinguish clearly the different forms. Suffice it to say for the present, that after comparing the histological appearances described by various authors of the changes in herpes zoster, herpes labialis and genitalis (all available), with some of my own cases herewith reported, and making due allowances for the different stages of the processes studied, I am not able to find any constant distinguishing characters by which the skin lesions of the various clinical forms of herpes may be separated.

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[1] Reference Handbook of the Medical Sciences, 1902, vol. iv.

I have recently had the opportunity of studying two cases which throw some light upon several points of importance in the pathology of herpes. The first case occurred in the private practice of my friend Dr. Edward F. Cushing, who recognized its interest and importance and obtained the autopsy. I take this opportunity of expressing my thanks to Dr. Cushing for the autopsy and for the use of the clinical history of the case. This case illustrates the causal relation between acute infections and herpes zoster, and emphasizes the identity of the lesions of the skin and nervous system in primary and secondary herpes of the trunk.

CASE I. *Summary.* Bronchitis, acute croupous pneumonia of both lungs, herpes zoster of the left side, distributed on the back and side (sixth dorsal), and the abdomen (eleventh dorsal); congestion and hemorrhage into the capsular and interstitial tissue at one side of the eleventh dorsal ganglion, with slight cellular infiltration and destruction of a few ganglion cells; amylaceous and hyaloid bodies in another portion of the same ganglion. Slight chronic and acute interstitial nephritis, acute parenchymatous and interstitial hepatitis, acute splenic tumor, old pericardial adhesions, hypertrophy and dilatation of the heart; fibromyoma uteri.

Clinical History. Miss T., aged sixty-three years, had not been well for about one year. On October 10, 1901, she was taken sick with a cold in the head, which a few days later was followed by bronchitis. She then developed pneumonia of the lower lobe of the left lung. Later the whole of the left lung became consolidated. On the morning of October 24th there were the physical signs of consolidation of the lower lobe of the right lung. Coincidently with the consolidation of the lower lobe of the left lung there developed well-marked herpes zoster in the mid-dorsal region of the left side, extending from the middle line in the back to about the anterior axillary line, corresponding to Head's sixth dorsal area. During the last two days of life a similar eruption occurred on the abdomen, in the left umbilical and iliac regions (eleventh dorsal area; see autopsy protocol). Albumin was present in the urine. Death took place at 2.30 P.M., October 24, 1901. Autopsy six hours later. The autopsy was done hurriedly and under difficulties, at the home of the patient. The body measured 160 cm. long, was sparely built, except over the abdomen and lower portion of the back, where there was a considerable amount of fat. The body was cold, rigor mortis moderate. There were a few reddish discolored areas on the outer aspects of the legs. On the left side of the abdomen, situated in the outer and lower portion of the left umbilical and the upper portion of the left iliac regions there was an area, the size of the palm of the hand, studded with scattered pale-red or gray areas from 3 to 6 or 10 mm. in diameter. Some of these areas were elevated and covered with dry grayish-red material, while others showed a distinct loss of epidermis. No typical vesicles containing fluid were to be found, but the areas had the appearance of dried vesicles. In distribution this area corresponded with Head's eleventh dorsal area. A similar but narrow area extended from the middle line in the mid-dorsal region as far as the anterior axillary line under the nipple, corresponding to Head's sixth dorsal area. The areas here were larger and the process appeared older than that on the abdomen. No other lesions were found upon the surface of the body. There was no facial herpes.

Chest. The chest was fairly well shaped, the muscles and fat rather wasted.

Both pleuræ were free from adhesions, and the pleural cavities contained no fluid. The visceral pleuræ over considerable areas were covered with a thin layer of fibrin, and were red and lustreless.

Right Lung. The apex was free from puckering and thickening. The upper lobe on section was congested and markedly œdematous. The whole of the middle and a large part of the lower lobe were consolidated, airless, and of a grayish-red color, and granular appearance. The mucous membrane of the bronchi was congested.

Left Lung. The whole lung was consolidated, airless, of a gray or grayish-red color, and granular appearance. The bronchial mucosa was congested. The bronchial glands were pigmented, but free from tubercle.

Heart. The pericardium was adherent to the diaphragm over a large area. Firm fibrous adhesions obliterated the pericardial sac. The walls of both ventricles were thickened. The valves, the coronary arteries and veins, as well as the aorta and large arteries, were normal. The myocardium was pale, otherwise normal; the heart weighed 400 grammes.

Abdomen. The muscles and fat of the abdominal wall were of ordinary appearance. The left lumbar region was prominent. The stomach was distended with gas, the large and small intestines contracted.

Liver. The liver was of ordinary appearance and size. The edges were rounded, the surfaces smooth, consistency not increased. On section the lobules are visible, the surface pale. The gall-bladder and bile-ducts were negative.

Spleen. The spleen was twice the ordinary size. On section it was of a grayish-red color; the trabeculæ and Malpighian bodies visible; consistency decreased.

Kidneys. The kidneys were of about the same size and appearance. The capsules were adherent in places, the surfaces were somewhat granular and marked by a few old scars. On section the consistency was somewhat increased, the surfaces pale, the cortices thinner than ordinary. The arteries, pelvis, ureters, bladder, and adrenals appeared normal, as did the stomach and intestines.

The ovaries were small and tough to the touch. The uterus was considerably enlarged: the body was the seat of a globular fibroma the size of an orange.

Nervous System. The brain could not be examined, and the examination was confined to the lower portion of the spinal cord; from the tenth dorsal segment downward with the cord the eleventh and twelfth dorsal and first lumbar posterior ganglia of both sides were removed. It was not possible to go higher in the time available for the examination. There was an excess of cerebro-spinal fluid, which, however, was quite clear. The meninges were normal in appearance. The cord showed no lesions on section. The ganglia showed no macroscopic lesions, and no hemorrhages were found about the posterior roots or the nerves going from the ganglia.

Portions of the various organs, including the cord and the ganglia, were hardened in Orth's fluid. The ganglia were transferred to 96 per cent. alcohol after a few hours. Portions of various organs, including the skin, were also hardened in Zenker's fluid.

Bacteriological Examination. Cover-slip preparations from the lungs and pleuræ showed lanceolate diplococci in capsules. Cultures on blood serum and on glycerin agar from the lungs, heart's blood, liver, spleen, kidneys, and cerebro-spinal fluid remained sterile.

Histological Examination. Lungs. Sections from both lungs showed well-marked croupous pneumonia, with lanceolate diplococci in the alveolar exudate.

Liver. There was well-marked fatty degeneration of the liver cells, congestion of the capillaries, with marked round-cell infiltration about many of the portal systems. No focal necrosis and no bacteria were found in suitably stained sections.

Kidneys. There were scattered areas of chronic glomerulitis, with thickening of the capillaries and of Bowman's capsule, with but little atrophy of the neighboring tubules. The epithelial cells of the convoluted tubules showed cloudy swelling. With no apparent relation with changes in the glomeruli or tubules, there were numerous areas of round-cell infiltration ; most of these cells were of the plasma-cell type, but some were lymphocytes. There was no necrosis of the renal epithelium and no abscess formation. No bacteria were to be found.

Skin. Sections were made through both areas of herpes, and, with the exception that the lesions were more extensive in the older lesion (sixth dorsal region), the changes were the same. There were few unbroken vesicles, but in most places the surface of the lesion was covered with amorphous and fibrillated fibrin containing a larger or smaller number of desquamated, swollen, and often disintegrating and necrotic epithelial cells. Some of these cells had undergone coagulation, and others liquefactive necrosis. In some places the cells of the deeper layer of the epidermis were markedly swollen, vacuolated, and evidently dropsical. In the fibrin and among the epithelial cells on the surface there were variable, often great, numbers of polymorphonuclear neutrophilic leucocytes. In some places there were cavities formed by the elevation of the superficial or subcorneal layer of epithelium. These were of considerable size in places, but were not numerous. Other small vesicles occurred in the exudate, their walls being formed by necrotic cells. Still other vesicles were between the epidermis and the underlying papillary layer. These were always small. In many places the papillary layer was exposed by the total destruction of the epidermis, and was covered by the exudation. In the papillæ and in the upper layer of the corium the veins and capillaries were markedly dilated, and in places there was hemorrhage, either into the tissue or upon the surface.

The papillæ and the upper layers of the corium showed other intense changes, coagulation necrosis, with hyaline and fibrinoid changes, nuclear fragmentation, and infiltration, with large numbers of polymorphonuclear neutrophiles, lymphocytes, and some plasma cells. Here and there a few eosinophiles were to be seen. This cellular infiltration was both diffuse and along the bloodvessels. Many of the sweat glands and hair follicles were swollen and distended with leucocytic and serous exudate. The epithelial cells were commonly swollen, granular, and often desquamated and necrotic. About many of these glands there was well-marked leucocytic infiltration, a few of the cells being eosinophiles. Scattered collections of leucocytes were also seen in the deeper layers of the skin. No bacteria were to be found in any of the lesions in sections stained by Weigert's fibrin method or with eosin and methylene blue.

The whole appearance of the lesion points to rapidly necrotic and exudative processes.

Posterior Root Ganglia. Sections were cut of the eleventh and twelfth dorsal and first lumbar ganglia of both sides and stained by Nissl's, Weigert's, and Marchi's methods, as well as with methylene blue and eosin, and hæmatoxylin and eosin. Sections from all the ganglia studied, except the eleventh dorsal of the left side, were entirely normal.

In sections of the latter ganglion changes were found in two places: (1) at one side of the ganglion about midway of its length, and (2) at the peripheral end.

1. In the sections cut transversely through about the middle of the ganglion at one side there was considerable hemorrhage, with pigmentation, into the capsule. In some of the sections corresponding to the area of capsular hemorrhage there was just beneath the capsule marked congestion of the capillaries and interstitial hemorrhage between the ganglion cells. In several sections small areas of cellular infiltration about destroyed ganglion cells were found. The ganglion cells elsewhere stained well and appeared normal.

2. At the peripheral end of the ganglion there were a number of amylaceous and hyaloid bodies, both singly and in groups, of the size and shape of ganglion cells, and lying in spaces similar to ganglion cell spaces. Many of these bodies were finely granular, some of the granules staining pink with eosin, and others blue with toluidin blue. Many bodies stained diffusely pink with eosin, and some diffusely blue with blue dyes. In some a central nucleus was apparent, and many showed a concentric arrangement. In a few places hyaline masses were made out in lymph spaces and in blood capillaries. Hyaloid and amylaceous bodies were also found in unmistakable lymph and blood-vessels. The question whether or not some at least of these bodies represented degenerated nerve cells is difficult to answer. From careful study I am convinced that some of them were formed and lie in nerve cell spaces. No lesions of the peripheral nerve, the posterior nerve roots, or in the spinal cord, could be made out.

The interpretation of the pathological changes of the above case appear to be as follows:

Acute croupous pneumonia following bronchitis, with the ordinary parenchymatous changes of the liver and kidneys common in such cases, with the addition of acute interstitial hepatitis and nephritis; an herpetic eruption of certain cutaneous areas, the spinal root ganglion corresponding to one of which areas was shown to be the seat of definite lesions (congestion and hemorrhage of both the capsule and a small area of the interstitial tissue of the ganglion, with cellular infiltration about a few degenerated ganglion cells, with hyaloid and amylaceous bodies, in another portion of the ganglion).

It seems fair, in the light of our present knowledge, to attribute these various lesions to the toxins of the pneumococcus.

The failure to find degenerative changes in the cord, the posterior roots, and the peripheral nerve is in accord with observations of Head and Carpenter, who did not find changes in these organs in a case of herpes dying on the eighth day. They were present in a case dying on the thirteenth day.

Including the 5 cases of Lesser, Chandelux, and Dubler with the 16 cases of Head and Carpenter, there are 21 well-studied cases of herpes zoster of the trunk in which definite destructive lesions have been demonstrated in the posterior root ganglia, corresponding to the distribution of the herpetic eruption. Two of the 21 cases of Head and Carpenter involved the head, in 1 case the ganglion was not removed, and in 2 others, in which death took place in 139 and 240 days, respectively, no lesions of the nervous system were found. In all 9 of the acute cases (three to sixteen days after the appearance of the eruption), definite and unmistakable ganglionic lesions were found. Of these cases 2 had had acute infections (cystitis, with retention of urine in paraplegia, and acute bronchitis and tubercular pneumonia). In the 12 chronic cases in which death occurred in from 57 to 790 days after the herpes the sensory ganglia corresponding to the distribution of the eruption showed well-marked chronic changes.

Our next case shows that the changes in the skin and Gasserian ganglion in herpes of the lips and nose in pneumonia are identical with those occurring in herpes ophthalmicus, and in the skin and posterior root ganglia in both primary and secondary herpes zoster of the trunk. It is also, curiously enough, apparently the first case of herpes of this region in which changes have been sought for in the Gasserian ganglion.

CASE II. *Summary.* Acute croupous pneumonia in a bartender, aged forty-one years. Death on the sixth day of the disease. Two days before death well-marked herpes of the upper lip and the nose, being much more extensive on the left side.

Autopsy showed acute croupous pneumonia (gray hepatization) involving the whole of the right lung, with fibrinopurulent pleurisy of the left side, œdema and congestion of the left lung. Chronic fibrous obliterative pleurisy of the right side. Herpes of the upper lip and nose, most marked on the left side. Congestion of the veins about the origins of the superior maxillary branches of both Gasserian ganglia. Hemorrhage into the capsule and tissue, with interstitial cellular infiltration and compression and degeneration of the ganglion cells near the origin of the superior maxillary branch of the left Gasserian ganglion. A few small areas of cellular infiltration in the same part of the right Gasserian ganglion. Marked congestion of the veins of the neck and brain and of the cerebral sinuses. Pneumococcus in the right lung and left pleura.

Clinical History. For permission to use the clinical history of the following case I am indebted to the courtesy of my colleague, Dr. J. H. Lowman, in whose service in the Lakeside Hospital the patient was admitted February 6, 1902, complaining of pain in the right side of the chest, cough, and fever.

The patient was a male, aged forty-one years, white, and a barkeeper by occupation. His family history was without present interest.

Personal History. He did not recall having ever been sick before, and denied having had diphtheria, scarlatina, rheumatism, pneumonia, pleurisy, syphilis, gonorrhœa, typhoid and malarial fevers. Some time ago he injured his right temple by a fall, but the wound healed promptly and was followed by no clinical symptoms. He drank beer and whiskey to excess at times, and also used tobacco. He had been a barkeeper for twelve years.

Present Illness. He got his feet wet on the night of February 8th, and awoke the next morning with severe pain in the right side of the chest, but did not have a chill.

On admission he had the physical signs of consolidation of the lower portion of the right lung. The left lung was clear. The spleen was enlarged. Examination of the other organs was negative. The leucocyte count on February 8th was 19,000, and on February 9th 13,000 per cubic millimetre. On February 9th, the fourth day of the disease, there appeared a well-marked vesicular eruption over the upper lip and the outer surface, and in the vestibule of the left side of the nose. This eruption on the lip and the outside of the nose extended somewhat to the right side of the median line. The sputum contained lanceolate diplococci. By February 11th the whole right lung was consolidated, and numerous moist râles were to be heard over the left lung.

The patient was delirious. Death occurred suddenly at 1.15 P.M., February 11, 1902, on the fifth day of the pneumonia and the beginning of the third day of the herpetic eruption.

Autopsy One Hour after Death. Body warm, no rigor mortis. Body 165 centimetres long, well built, and well nourished. There were no marks, scars, or wounds on the body. On the upper lip, involving both mucous and skin surfaces, there were a number of dried crusts surmounting slightly elevated areas, with red margins. These areas varied from 2 to 5 millimetres in diameter. Similar papules and dried vesicles were present on the skin of the vestibule and external surface of the left side of the nose. Altogether there were from fifteen to twenty such areas. Several similar lesions were also found to the right side of the median line of the lip and nose. No other herpetic eruptions were to be found on the body.

Nervous System. The veins of the dura and pia arachnoid and all the sinuses were markedly congested; the pia arachnoid was smooth and glistening. The structures at the base of the brain were normal. The brain on section showed congestion, but was otherwise normal in appearance.

The Gasserian Ganglia. The veins near the ganglion were engorged with blood. The ganglion was of ordinary size. On the upper surface just below the entrance of the sensory root and between and about the exit of the ophthalmic and superior maxillary branches the veins were congested and stood out prominently. The same appearance was seen on the posterior surface, but the congestion was less well marked.

The Left Ganglion. The vessels about the ganglion were engorged, as were the veins about and between the origin of the ophthalmic and superior maxillary branches of the ganglion. About the root of the superior maxillary branch this was very marked, and there was also hemorrhage into the capsule at this part on the posterior aspect of the ganglion. The fifth nerve and the branches from both ganglia appeared normal. The cord and the posterior root ganglia were not removed.

Chest. The chest was well formed; the sternum, ribs, and costal cartilages were normal.

The right lung was bound down by old but thin adhesions; the pleural cavity was obliterated. The right lung was consolidated throughout. On section it was firm and airless, of a grayish color, and quite granular in appearance. The mucosa of the bronchi was congested, otherwise normal. The left pleural cavity contained about 100 c.c. of seropurulent fluid. The surface of the lower lobe was covered with a thin fibrinous exudate. The lung crepitated throughout. On section the lung was markedly congested and œdematous, but was free from consolidation.

The description of the other organs is without present interest, and will, therefore, be omitted.

Cover-slips from the right lung and left pleura showed encapsulated lanceolate diplococci.

Plate cultures from both lungs, the left pleura, and heart's blood and pericardium showed pneumococcus in pure culture. Similar cultures from the liver, spleen, kidneys, and gall-bladder remained sterile.

Histological Examination. Lungs. Sections of the consolidated area showed well-marked croupous pneumonia, with lanceolate diplococci in the exudate. Sections of the other organs, with the exception of the skin of the lip and nose and of the Gasserian ganglia, showed nothing of present interest.

Skin of Lip and Nose. Bits of tissue were cut out and hardened in formalin and 95 per cent. alcohol, and sections were stained in carbol-toluidin blue and eosin, hæmatoxylin and eosin, and by Weigert's fibrin method.

The changes found were practically identical with those from the herpetic areas of Case I.

As in Case I., few well-developed vesicles remained, the surface of the lesions, as a rule, being covered with a crust of amorphous and fibrillated fibrin and fibrinoid material containing desquamated and often necrotic epithelial cells, polymorphonuclear and mononuclear leucocytes, and cellular and nuclear fragments. Here and there rather small vesicles could be made out. As in Case I., some were elongated cavities in the exudate, or in the superficial layer of the skin, just beneath the horny layer, while others were between the underlying inflamed papillæ and the epidermis. Most of the latter cavities were small, and their walls were formed of necrotic epithelium and their floors of the naked papillæ. In some places ballooning of the cells of the epidermis could be made out. In many places the margin between the necrotic and the unchanged epidermis was rather clear cut, but in some places near the necrotic portions the small vesicles could be made out in the neighboring otherwise normal epidermis. In most places at the site of the lesion the whole thickness of the epidermis was necrotic.

Beneath the fibrinous layer there were, in all sections examined, changes in the epithelium, marked coagulation and liquefactive necrosis, and hyaline transformation of the cells. The papillary layer and outer part of the corium were similarly affected. There was, in many places, marked nuclear fragmentation. The epithelium of the sweat glands and some of the hair follicles, when present, showed changes—swelling and liquefaction, and often a reticular appearance. Some cells were markedly swollen, many cells showed coagulation necrosis. Many nuclear fragments were to be seen. The bloodvessels, especially the capillaries and small veins of the papillæ and corium, were markedly dilated. Some were crowded with leucocytes. In some of the superficial vessels there were thrombi composed of pink-staining material. The papillæ and the superficial portions of the corium were diffusely infiltrated with great numbers of polymorphonuclear, neutrophilic, and large and small mononuclear leucocytes, and some plasma cells. The leucocytic infiltration could also be traced along some of the small vessels into the deeper layers of the corium. About some of the superficial veins and capillaries often large numbers of red blood cells had escaped into the tissue. Some of the lymph spaces were dilated. The lesions here, as in the herpes of Case I., were both degenerative and exudative, and involved both epidermis and corium. No inflammatory changes were found in nerves in the skin. No bacteria were found in the lesions of the skin, but in the superficial part of the fibrinous exudate, in sections taken from the vestibule of the nose, diplococci and some bacilli, morphologically like B. mucosus capsulatus, were found.

Gasserian Ganglia. The ganglia with the fifth nerve roots and the origins of the ganglionic branches were hardened in formalin (10 per cent. solution).

The two ganglia were mounted in celloidin, side by side, on the same block and cut in serial sections, every other section being stained and mounted in order. Many of the alternate sections were also stained.

In mounting on the block the left ganglion was at a somewhat higher level than the right, so in the parallel sections as mounted for histological study the two ganglia were not identical in structure, but as the series was followed to the end the right ganglion was found to be similar to the left in structural detail.

Left Gasserian Ganglion. In sections 1 to 8 there were no ganglion cells near the superior maxillary branch. The veins about this branch were enormously dilated and filled with red blood cells. In some places in the largest vein there were collections of leucocytes and larger and smaller granular masses, suggesting fibrin. No changes were found in the opposite end of the ganglion. About the dilated veins there was hemorrhage into the pia or capsule of the ganglion. In section 9 a small oval bit of ganglion tissue, containing ganglion cells, became apparent near the superior maxillary branch. In sections 9, 10, 11, and 12, corresponding to this, there were capsular and subcapsular hemorrhage, with compression of the superficial ganglion cells. In sections 15 to 35 the small strip of ganglion tissue in relation with the superior maxillary branch became very much larger, and formed an elongated strip of tissue traversing the thin portion of the ganglion, reaching from the side of the superior maxillary branch to, but not uniting with, the larger ganglionic mass corresponding to the origin of the inferior or third branch. About the middle of this strip there was marked congestion of the veins about the superior maxillary branch, into and, here and there, just beneath the capsule of the ganglion. This congestion and hemorrhage must have compressed the ganglion cells in this region. Sections 36 and 37 showed the first well-marked changes in ganglion cells and interstitial tissue. About the central portion of this strip of ganglion tissue some of the ganglion cells were vacuolated, others were very pale, non-granular, homogeneous, and stained poorly. The nuclei showed no special changes. Some ganglion cells were evidently necrotic, the cytoplasm staining diffusely, and the nuclei being displaced to one side. Here, especially about the changed ganglion cells, there was marked cellular infiltration, with plasma cells, lymphocytes, and polymorphonuclear neutrophiles.

These cells were both in the interstitial tissue and grouped about changed ganglion cells, which were evidently compressed thereby. In places there had evidently been a proliferation of the endothelial cells about the ganglion cells.

In sections 40 to 60 the congestion and hemorrhage were noticeable, the cellular infiltration being inconspicuous.

Beginning in section 73, cellular infiltration became marked again. In section 77, in the above-mentioned strip of ganglion tissue involving an area of from twenty to twenty-five ganglion cells, there was marked cellular infiltration with interstitial hemorrhage. Some of the ganglion cells were necrotic. Smaller areas of interstitial cellular infiltration were found near this area.

Section 78, showed, at the border of the same hemorrhagic area a group of degenerated ganglion cells surrounded by large numbers of lymphocytes, plasma cells, and polymorphonuclear leucocytes, red blood cells, and proliferated endothelial cells of the pericellular spaces. The ganglion cells of the affected area showed the same changes described above; many have entirely disappeared. They seemed to have been compressed and destroyed by the interstitial exudate and hemorrhage. A few ganglion cells in this area were the seat of large vacuoles. Nuclear figures could be made out here and there in the cells of the interstitial infiltration. In most of the sections from 60 to 85 these changes were more or less well marked. The area of hemorrhage could be traced in them all. The changes in the left ganglion were lost after the 95th section.

Right Gasserian Ganglion. All the sections cut showed congestion of the veins and capillaries about the second or superior maxillary branch, as described for the right ganglion. Hemorrhage was, however, absent. In sections 80 to 95 a few areas of cellular infiltration were found in the area corresponding to that showing similar changes in the left ganglion.

These areas of cellular infiltration were small and scattered, and nothing like so well marked as those found in the left ganglion. In both ganglia a considerable number of amylaceous and hyaloid bodies were found in the lymph spaces.

In preparations of the fifth nerve, and of the superior maxillary branches of both sides, made by Marchi's method, no degenerations were to be found.

No bacteria were found in the ganglia or in the dilated veins.

That herpes zoster, following some part of the distribution of the trigeminal nerve is due to changes in the Gasserian ganglion is supported by observations on four previous cases.

Wys, in 1871 (quoted by Head and Carpenter), reported a case of herpes zoster involving the distribution of the whole of the first division of the trigeminal nerve ; the patient died on the seventh day of the eruption. There were thrombosis of the ophthalmic vein, abscesses of the eye muscles, and purulent infiltration of the connective tissue of the eyeball. There was hemorrhage about the origin of the ophthalmic division and about the inner side of the ganglion. Microscopically, there was extravasation of blood into the ganglion and into the first division of the nerve, with purulent inflammation of the ganglion.

Sattler, in 1875 (quoted by Head and Carpenter), reported a case of herpes ophthalmicus of the right side, in a man, aged eighty-five years, occurring some days after carbonic oxide gas poisoning. Death occurred fourteen days afterward. In the corresponding Gasserian ganglion there was destruction of ganglion cells and small-cell infiltration. The ophthalmic branch of the nerve showed degeneration, the other branches being normal.

Head and Carpenter reported a case of herpes of the right frontal region in which, one hundred and ninety days later, at autopsy, they found hemorrhage and destruction of ganglion cells in the right Gasserian ganglion.

In another case these authors studied the right Gasserian ganglion thirty days after an attack of herpes of the chin and cheek of the right side of the face (third division). "In that portion of the right ganglion which receives the fibres of the inferior maxillary branch of the nerve" there was congestion of the bloodvessels, destruction of ganglion cells, and cellular infiltration. Degenerated fibres were found in the fifth nerve central to the ganglion, in the pons and medulla, as well as in the inferior maxillary division of the fifth nerve.

Both of the last two cases were subjects of general paralysis. Wys' case was apparently spontaneous, while that of Sattler followed carbonic oxide gas poisoning. As far as I am able to find, these comprise all the observations on the relation between changes in the Gasserian ganglia and herpes distributed along the course of the trigeminus. Of these four cases, three were examples of ophthalmic herpes, and one of inferior maxillary herpes. I am not aware that the relation of the changes in the Gasserian ganglia to herpes of the upper lip and nose, occurring either spontaneously or in the course of pneumonia, malaria, cerebro-spinal meningitis, gastro-intestinal disorders, and other infections and intoxications, has been investigated.

I wish to call attention to the practical identity of both the lesions of the skin and of the nervous system in these two cases of herpes, the one of the trunk, and the other of the upper lip and nose, both occurring during the course of acute croupous pneumonia. Reference to the detailed descriptions will, I think, show that the lesions agree in all important particulars, and only differ in severity. The extent and severity of the skin lesions are also in definite relation to those of the corresponding ganglia. The skin and ganglion changes in Case II. (trigeminal distribution) were more severe than in Case I. (dorsal 11). One is forced to the conclusion that the herpes of the trunk and the herpes of the lip and nose occurring in these two cases are identical clinically, histologically, and probably etiologically. They further demonstrate that the ganglionic lesions of herpes zoster of the trunk and herpes of the lip and nose occurring in pneumonia are identical with those described by previous observers for herpes zoster of the trunk and extremities and herpes distributed along both the first and third divisions of the trigeminus, occurring both spontaneously (idiopathic herpes), and secondarily to acute infections, as cystitis, bronchitis, acute tubercular pneumonia (Head and Carpenter), after poisons, as carbonic oxide gas (Sattler), and the invasion of tumors (Head and Carpenter). As far as I have been able to learn, no anatomical studies have been made on the lesions of the nervous system in herpes of the lip and nose occurring in malaria and other continued fevers, in pneumonia, cerebro-spinal meningitis, coryza, or gastro-intestinal disorders. We are also without similar observations in genital herpes. In the case of the latter, however, Unna's description of the skin lesions, based on observations in three cases, is practically identical with his findings in a case of herpes labialis in an individual dead of a continued fever, with these lesions of our cases and with those found by Head and Carpenter and others in herpes zoster. Unna, however, found marked ballooning of the epithelial cells of herpes zoster (trunk ?), a condition not found by him in herpes genitalis and his one case of herpes labialis.

In our case of labial and nasal herpes, in some places the swelling and liquefaction of the epithelial cells, especially in the hair follicles, was better marked than in the case of herpes of the trunk. It seems likely that in a necrotic and exudative process passing rapidly through different stages the changes would not be uniform in the lesions of each and every case. All that can be said at present is that the skin lesions of our two cases are identical and agree with those described by most authors.

Though there are no previous observations on the relation of changes in the nervous system in herpes labialis and nasalis occurring in pneumonia, and none at all in malaria, for the third acute infectious process in which herpes is common there are some most interesting and suggestive data. I refer to epidemic cerebro-spinal meningitis. In their monograph on this disease, Councilman, Mallory, and Wright[1] call attention to the frequent occurrence of herpes of both the lips and nose, and to the fact that it may appear on other parts of the face and even elsewhere on the body; and in the summary on page 163 they state that "in its (the infection) extension along the fifth nerve it produces an acute inflammation of the Gasserian ganglion, with destruction and degeneration of the nerve cells composing it." On page 114 they state that sections were made of the Gasserian ganglia in five cases and of the spinal ganglia in two. The Gasserian ganglia in acute cases were "infiltrated with pus, and masses of ganglion cells were often separated from their connection." There was more or less hemorrhage; some ganglion cells were small and some devoid of nuclei; some cells contained large vacuolar spaces. Diplococci were found in some sections. In the more chronic cases the amount of leucocytic infiltration was less, but there was marked proliferation of the interstitial tissue, and in one case there was œdema, with marked cellular infiltration, especially about the ganglion cells, lymphoid, epithelioid, and plasma cells being found. There was atrophy, often going on to complete necrosis of the cells (ganglion cells). The spinal ganglia were not equally affected, but all seemed somewhat swollen and œdematous. On microscopic examination much the same changes were found in these as in the Gasserian ganglia. Degenerative changes were, of course, to be found in the nerves. They also showed that these changes may occur rapidly, for purulent infiltration was observed in the ganglia of a goat twelve hours after inoculation of the diplococcus intracellularis meningitidis into the spinal cord.

On page 125 they state that in one case the herpetic vesicles on the lip were examined. In them there was extensive infiltration, with pus cells in the tissue around the vessels, and proliferation of the fixed cells of the tissue. No mention is made of the epithelium; no diplococci were found in the pus cells.

Unfortunately no statement is made concerning the presence or absence of herpes of either the head or the trunk in the cases showing lesions of the Gasserian and spinal ganglia. In the one case showing skin lesions (small, dark purplish spots on the trunk and extremities) coming to autopsy they found congestion and dilatation of the blood-vessels of the skin, with hemorrhage in places, and in some places proliferation of the cells about the vessels. In the centre of the hemorrhagic area there was some infiltration with pus cells, and in one place the upper layers of the epithelium were slightly elevated by the accumulation of pus cells beneath.

These observations furnish at least ample explanation for the occurrence of herpes of both the head and trunk in meningitis. The influence of the changes in the ganglia upon the other changes in the skin are, of course, only conjectural.

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[1] Report of the State Board of Health of Massachusetts, 1898.

ETIOLOGY OF HERPES. From what has gone before, it is evident that the lesions of the skin and nervous system of primary, or idiopathic, or spontaneous herpes zoster of the head, neck, trunk, and extremities are the same, as are also the same lesions in certain cases of herpes of the trunk and face (upper lip and nose) occurring in pneumonia (Howard), and similar lesions of the nervous system in herpes of the trunk occurring in acute cystitis in a man with paraplegia, acute bronchitis ; pernicious anæmia in a patient who had taken arsenic, and after the invasion of a lymphosarcoma (Head and Carpenter), and finally in ophthalmic herpes after poisoning with carbonic oxide gas (Sattler).

Primary herpes zoster is regarded by Head and Carpenter, and by Van Harlingen[1] and others, as an acute specific infectious disease due to an unknown cause, having a selective affinity for certain sensory ganglia in which certain degenerative, destructive and often inflammatory lesions are produced. These lesions in some unknown way cause acute degenerative, exudative, and proliferative changes in the skin and mucous, and possibly serous, membranes corresponding to the nerve distribution of the affected ganglia. There is a considerable amount of evidence in favor of the hypothesis that there is an acute specific infectious process of this nature, but no convincing proof has been so far adduced in its support.

It must be further borne in mind that there is a large group of cases of herpes either following the action of known toxins (carbonic oxide gas and arsenic), the involvement of the ganglia by tumors, or occurring in the course of certain infections, as pneumonia, malarial and typhoid fevers, and cerebro-spinal meningitis (in which, as has been shown, there are often intense lesions of the sensory ganglia), in all of which the lesions, as far as is known, are identical. Herpes, like pneumonia, meningitis, and inflammation in general, is a pathological condition, with definite lesions, capable, however, of being excited by a variety of causes, and is not always produced by the same causes; an efficient cause being one producing compression, degeneration, or destruction of ganglion tissue. It is not improbable that the primary lesions are often due directly or indirectly to the soluble toxins of various micro-organisms. The special frequency of labial and nasal herpes, and of herpes of the head and face in general, in malaria, pneumonia, and cerebro-spinal meningitis, is readily explained. In the case of malaria the organisms in the circulating blood often accumulate in the brain, where the Gasserian ganglia may be readily affected by congestion, the action of toxines, or even by capillary thrombi of parasites. In pneumonia, the organisms or their toxines may locate in the ganglia. What, however, to my mind seems the most reasonable predisposing cause of the frequent occurrence of labial and nasal herpes in this disease is the marked passive congestion which is so often present. This was especially noticeable in Case II., in which there was marked congestion of not only the bloodvessels and sinuses of the brain and meninges, but of the vessels of and near the Gasserian ganglia themselves, and especially about the second division. This marked congestion, which favors hemorrhage, the action of the toxines, poisons, and organisms in the blood, and thrombosis, may probably of itself, by pressure and by interfering with nutrition of the ganglion cells, cause degeneration sufficient to excite the herpetic changes.

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[1] THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, January, 1902.

As Councilman, Mallory, and Wright have shown, in epidemic cerebro-spinal meningitis, the spinal sensory ganglia, and especially the Gasserian ganglia, are often the seat of extensive changes due to the extension of the infection along nerve sheaths to these ganglia.

There is, *a priori*, no reason why changes in these ganglia should not occur in bronchitis and pleurisy. There is also no reason why the peripheral lesion in herpes zoster should not affect the pleura, as suggested by Curtin, just as the same process is known to affect the mouth, cheek, and pharynx. We know nothing in regard to the relation of lesions of the nervous system to the so-called simple herpes (with which labial and nasal herpes of pneumonia, malaria, and epidemic cerebrospinal meningitis have hitherto been included) of the face, especially of the lips and nose, occurring in coryza, gastro-intestinal disorders, and the herpes genitalis.

It is to be hoped that observations will be made on this point, and it is not impossible that some cases, at least, will fall in the class we have been considering.

The question why should the peripheral changes occur after the lesions of the nervous system found in herpes is a difficult one to answer. There is no evidence that the skin lesions are due to the local presence of parasites, infection with which is predisposed by the nerve lesions.

Head and Carpenter are " inclined to think that the trophic disturbances of the skin are an extreme form of activity of the same cells, disturbance of which by afferent impulses along the white ramus produces the hyperalgesia that accompanies visceral referred pain ;" but they " do not imagine that the eruption of herpes zoster is produced by disturbance of special trophic nerves, but by intense irritation of cells in the ganglion which normally subserves the function of pain, and more particularly that form of pain produced by afferent visceral impulses."

This is, however, far from explaining why irritation of these ganglion cells and nerve fibres causes a severe inflammatory process marked by intense vascular changes, cell destruction, exudation, and proliferation. The presence of hyaline, granular, and apparently red blood cell thrombi in many of the dilated bloodvessels of the herpetic areas in my cases is of interest, and may account for the hemorrhage, but were hardly extensive enough to explain the necrosis. What was the origin of these thrombi? Were they associated with changes in the vascular endothelium due to nerve changes? Were the hemorrhage and exudation due, in part, to the increased permeability of the vessel walls, the result of loss of nerve control or nerve irritability? These are some of the questions awaiting solution.

CONCLUSIONS. 1. Herpes zoster is a pathological condition, like pneumonia, for instance, with definite lesions of certain sensory ganglia, sensory nerves, and the skin, capable of being excited by a variety of causes. It is probable that the primary ganglionic lesions are commonly due directly or indirectly to the soluble toxines of various micro-organisms. The skin lesions may be on the head, neck, trunk, or extremities, corresponding to the Gasserian and posterior root ganglia affected.

2. Various forms can be distinguished. *a.* Spontaneous or primary herpes, thought by Head and Carpenter, and others, to be a specific infectious disease, the specific causal agent of which has a special affinity for certain sensory ganglia (posterior spinal and Gasserian). *b.* Herpes occurring after certain definite toxic agents, as arsenic and carbonic oxide gas, etc. *c.* Herpes occurring in the course of certain acute infectious diseases, as pneumonia, cerebro-spinal meningitis, and probably of malarial and typhoid fevers. The lesions of the ganglia and of the skin in the above three forms are the same, and the processes, therefore, presumably identical. *d.* Herpes simplex, so-called, affecting the lips and nose in coryza, gastro-intestinal intoxications, etc., and genitals (herpes genitalis) has not been sufficiently investigated to be classified; no evidence exists for or against its connection with changes in the nervous system.

3. As far as changes in the skin in herpes are concerned, they are illustrations of particular forms of necrosis and inflammatory reaction, and, as in similar lesions in other organs, can probably be excited in a variety of ways.

4. Herpes should be classified according to its relation to changes in the nervous system, and to this end every possible opportunity should be embraced for extending our knowledge in this direction.